Study Protocol Cover Page

Official Study Title:	OPSIS: A Phase IIa, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of STN1013600 Ophthalmic Solution 0.1% and 0.3% Compared with Placebo in Subjects with Presbyopia
NCT Number:	NCT05665387
Date of the document:	23 SEPT 2022

PROTOCOL 101360002IN

Protocol Title: OPSIS: A Phase IIa, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of STN1013600 Ophthalmic Solution 0.1% and 0.3% Compared with Placebo in Subjects with Presbyopia

Protocol Number: 101360002IN

Compound: STN1013600 Ursodeoxycholic Acid, UCDA (DE-136)

Study Phase: Phase IIa

Sponsor Name: Santen Inc.

Legal Registered Address: 6401 Hollis Street, Suite 125, Emeryville CA 94608, USA

Regulatory Agency Identifier Number(s): IND Number: 153534

Protocol Version / Approval Date: Original / 23 September 2022

I have read the **101360002IN** protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and have complied with all financial and administrative requirements of the governing body of the clinical institution and Santen as the Sponsor. I will obtain written informed consent from each study subject prior to performing any study-specific procedures. I understand that my electronic signature on an electronic case report form (eCRF) indicates that the data there in has been reviewed and accepted by me as the investigator.

INVESTIGATOR:

Date: _____

Signature: _____

Name: _____

Address: _____

_____

Phone: _____

This study will be conducted in accordance with applicable Good Clinical Practices (GCP), United States Code of Federal Regulations, International Conference on Harmonization (ICH) guidelines, and the Declaration of Helsinki.

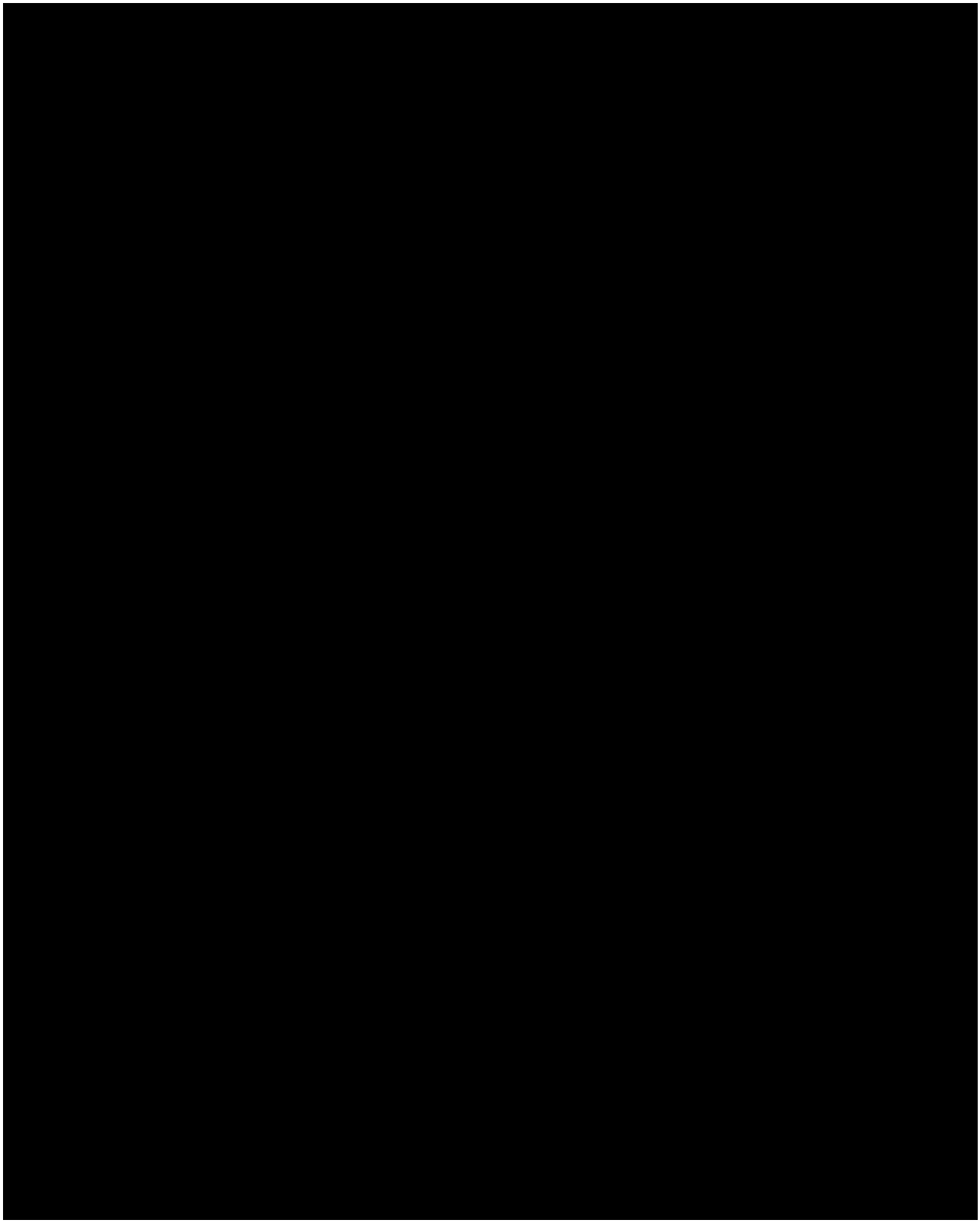


TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company:
Santen Inc.
6401 Hollis Street, Suite 125
Emeryville, CA 94608, USA

Name of Investigational Product:
STN1013600 Ophthalmic Solution

Name of Active Ingredient:
Ursodiol, Ursodeoxycholic acid (UDCA)

Title of Study: OPSIS: A Phase IIa, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of STN1013600 Ophthalmic Solution 0.1% and 0.3% Compared with Placebo in Subjects with Presbyopia

Protocol Number: 101360002IN

Number of Subjects (Planned): Approximately 75 subjects with Presbyopia.

Study Center(s): Approximately 13 Sites in the United States

[redacted]

Study Period: Approximately 6 months	**Phase of Development:** Phase IIa

Study Objectives and Endpoints:

Study Objectives	**Corresponding Study Endpoints**
Primary Efficacy Objective: To assess the efficacy of two concentrations of STN1013600 ophthalmic solution (0.1% and 0.3%) twice daily dosing when compared to Placebo in subjects aged from 47 to 55 years with presbyopia.	**Primary Efficacy Endpoint:** • Mean change from baseline in Binocular DCNVA at Month 2

Secondary Efficacy Objective: To assess the dose response of STN1013600 ophthalmic solution.	**Secondary Efficacy Endpoints:** • Mean change from baseline in Study Eye DCNVA at all visits • Mean change from baseline in Binocular DCNVA at all visits • Proportion of subjects who improve 1/2/3-lines or more in Study Eye and Binocular DCNVA at each visit • Mean change from baseline in quality of life assessed with Near Activity Visual Questionnaire (NAVQ) at Month 2 and Month 3 • Subject treatment satisfaction as assessed by Patient Global Rating of Treatment at Month 2
Safety Objective: To assess the safety of two concentrations of STN1013600 ophthalmic solution (0.1% and 0.3%) twice daily dosing when compared to Placebo in subjects aged from 47 to 55 years with presbyopia.	**Safety Endpoint:** • Safety of STN1013600 will be assessed by adverse events (AEs), Intra-ocular Pressure (IOP), slit-lamp bio-microscopy, ophthalmoscopy, and laboratory tests (serum chemistry, hematology, and urinalysis).
[redacted]	[redacted]

Duration of Treatment: 2 months, and 1 month of follow up without treatment.

Methodology:

This is a Phase IIa, randomized, double-masked, placebo-controlled, parallel-group study assessing the efficacy and safety of STN1013600 ophthalmic solution (0.1% and 0.3%) in subjects with Presbyopia.

Subjects with Presbyopia who meet all eligibility criteria at Visit 1 (Screening) will be randomized at Visit 2 (Baseline) to receive treatment for 2 months.

Approximately 75 subjects who meet all eligibility criteria at Visit 1 (Screening) will be randomized at Visit 2 (Baseline) in a 2:2:1 ratio to one of the following three treatment arms:

- 0.1% STN1013600 ophthalmic solution BID (08:00 & 20:00 ± 60 min)
- 0.3% STN1013600 ophthalmic solution BID (08:00 & 20:00 ± 60 min)
- Placebo (Vehicle) BID (08:00 & 20:00 ± 60 min)

Subjects will be treated for 2 months, followed by a 1-month safety follow-up without treatment.

Study Design: (Refer to Figure 1)

This study will consist of a Screening Period of up to 15 days, followed by a 2-month Treatment Period and subsequently 1-month Treatment-free follow-up Period.

At the Visit 1 (Screening), subjects will be screened against the inclusion and exclusion criteria and if subject meets all eligibility criteria, subjects will proceed to Visit 2 (Baseline).

Per study design, subjects who qualify per eligibility criteria will be treated bilaterally (both eyes).

The study eye will be the eye that qualifies with the worse DCNVA per eligibility criteria at Visit 2. If both eyes have the same DCNVA, the right eye will be designated as the study eye.

Treatment Period (2 months):

At Visit 2 (Baseline), approximately 75 eligible subjects will be randomized to receive either 0.1% STN1013600 ophthalmic solution BID or 0.3% STN1013600 ophthalmic solution BID or Placebo BID in a 2:2:1 ratio. Subjects will be treated for 2 months with scheduled assessment visits at [redacted]

At Visit 2 (Baseline), subjects will administer their first dose of study medication (study eye drops) as per their assigned/randomized study treatment at 20:00 (± 60 min). The next day (Day 2), subjects will subsequently dose with their assigned study medication at 08:00 & 20:00 (± 60 min) and continue dosing through Visit 6 (Month 2).

Treatment-free Follow-up Period (1 month):

After Treatment Period, subjects will be followed for 1 month with scheduled study assessment (including safety assessments) visits at Visit 7 (Month 3).

Pharmacogenomics/Genomics:

Not applicable

Santen Steering Committee:

An internal Santen steering committee (SSC) whose members will not be participating in the OPSIS study conduct will serve as an advisory board to the Santen senior management team. [redacted] The [redacted] verning charter.

Masking:

This is a double-masked study. The subjects, Investigators, Examiners and Santen personnel involved in the conduct of the study will be masked to the study treatments. An authorized unmasked study staff member at the investigator site who is not the Investigator or Examiner will dispense and collect study medication(s). Patient medication compliance diary will be reviewed.

Subjects will be instructed not to show the bottles or discuss the eye drops to either the Masked Investigator or the Masked Examiner or other study subjects.

[redacted]

Inclusion criteria:

Participants are eligible to be included in the study only if all of the following criteria apply:

1. [redacted]
2. Phakic presbyopic subjects, Male or Female between 47 and 55 years of age.
3. Distance-corrected near visual acuity (DCNVA) for each eye, as well as for binocular vision, 70 EDTRS letters or worse (equivalent to 0.3 logMAR or worse; or 20/40 Snellen or worse) at 40 cm. To be reconfirmed at Visit 2 (Baseline).
4. Best-corrected distance visual acuity (BCDVA) for each eye of 85 ETDRS letters or better (equivalent to 0.00 logMAR or better; or 20/20 Snellen or better) at 4 m. To be reconfirmed at Visit 2 (Baseline).
5. [redacted]

6. [redacted]
7. [redacted]
8. [redacted]

Exclusion Criteria:

Participants are excluded from the study if any of the following criteria apply:

Ocular Conditions:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted]
8. [redacted]
9. [redacted]

10. [redacted]
11. [redacted]
12. [redacted]
13. [redacted]
14. [redacted]
15. [redacted]
16. Secondary cause of presbyopia in either eye as assessed by investigator (*e.g.,* damage to lens, zonules or ciliary muscle, multiple sclerosis, cardiovascular accidents, vascular insufficiency, myasthenia gravis, anemia, influenza, measles).
17. Any history of ocular surgery (including ocular laser surgery) in either eye or plan of ocular surgery (including ocular laser surgery) during the course of the study.
18. Prior invasive therapy for presbyopia (*e.g.,* ciliary body electrostimulation, corneal implants).
    - Prior medical therapy for Presbyopia (*e.g.*, supplements, miotic medications, training exercises) within 30 days of Visit 1 (Screening)
    - Subjects with prior non-surgical optical correction (*e.g.,* corrective eyeglasses) are eligible for the study

Concomitant Medications:

19. [redacted]
20. [redacted]
21. [redacted]
22. [redacted]

Non-Ocular Conditions:

23. [redacted]
24. [redacted]
25. [redacted]
26. [redacted]
27. [redacted]
28. [redacted]
29. [redacted]
30. [redacted]
31. [redacted]
32. [redacted]
33. [redacted]

Reference Therapy, Dosage and Mode of Administration:

Subjects will be randomly assigned 2:2:1 ratio to one of three treatment arms to receive either: 0.1% STN1013600 ophthalmic solution BID (08:00 & 20:00 ± 60 min), 0.3% STN1013600 ophthalmic solution BID (08:00 & 20:00 ± 60 min), or placebo (vehicle) BID (08:00 & 20:00 ± 60 min) as described below:

Investigational Product:

0.1% STN1013600 ophthalmic solution contains 0.1% STN1013600. [redacted]

0.3% STN1013600 ophthalmic solution contains 0.3% STN1013600. [redacted]

Vehicle:

The vehicle is identical to the investigational product but does not contain the active ingredient STN1013600.

Route of Administration of Investigational Product: Topical ocular

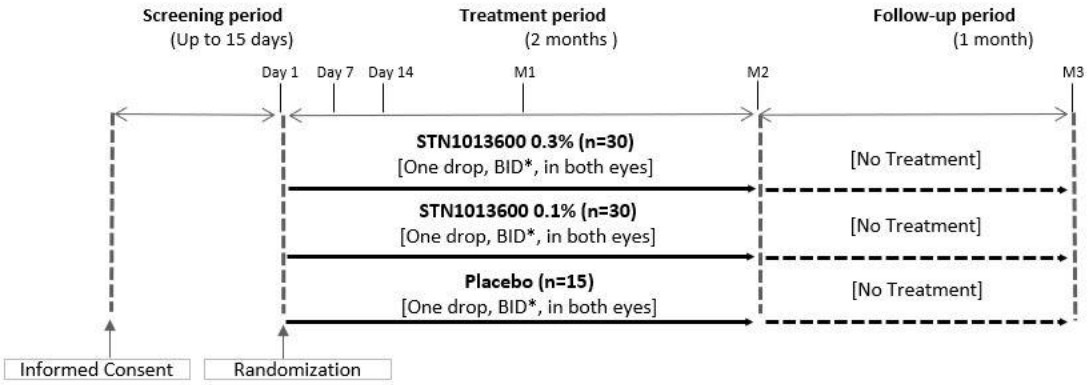
Statistical methods:

[redacted]

An interim analysis may be performed when the first 40 subjects complete Day 14 Visit. There are two goals for this interim analysis: (1) to assess for futility and (2) to assess for efficacy. More details on the interim analysis plan will be provided in the SAP.

1.2. Schema

Figure 1: Study Design Schema



[redacted]

1.3. Schedule of Assessments (SoA)

Table 2: Schedule of Assessments

		Treatment Period					Follow Up Without Treatment
Study Procedures	**Visit 1 / Screening Up to 15 days Before Day 1**	**Visit 2 Baseline / Day 1**	**Visit 3 Day 7 ± 2 Days**	**Visit 4 Day 14 ± 2 Days**	**Visit 5 Month 1 ± 3 Days**	**Visit 6 Month 2 ± 3 Days**	**Visit 7 Month 3 ± 3 Days/ Early Discontinuation**
Informed consent[a]	X						
Inclusion and Exclusion criteria	X	X					
[redacted][b]	[redacted]						
[redacted][b]		[redacted]					
Demographic information	X						
Ocular and systemic medical history	X						
Vital Signs (Blood Pressure, Heart Rate, Temperature)	X	X	X	X	X	X	X
Height and weight	X						
Previous and current concomitant ocular and systemic medications	X	X	X	X	X	X	X
[redacted]	[redacted]						[redacted]
[redacted]							
Distance Corrected Near Visual Acuity Test (40 cm)[d]	X	X	X	X	X	X	X
[redacted][d]		[redacted]					

Table 2: Schedule of Assessments (Continued)

		Treatment Period					Follow Up Without Treatment
Study Procedures	**Visit 1 / Screening Up to 15 Days Before Day 1**	**Visit 2 Baseline / Day 1**	**Visit 3 Day 7 ± 2 Days**	**Visit 4 Day 14 ± 2 Days**	**Visit 5 Month 1 ± 3 Days**	**Visit 6 Month 2 ± 3 Days**	**Visit 7 Month 3 ± 3 Days/ Early Discontinuation**
Best Corrected Distance Visual Acuity Test (4m)[d]	X	X	X	X	X	X	X
[redacted]		[redacted]					
[redacted]	[redacted]						
[redacted]		[redacted]					
Slit lamp biomicroscopy	X	X	X	X	X	X	X
Pupil size	X	X	X	X	X	X	X
[redacted]							
[redacted]	[redacted]						
Intraocular Pressure (IOP)	X	X	X	X	X	X	X
Ophthalmoscopy	X[g]	X	X	X	X	X	X[g]
Patient global rating of treatment						X	
Post-Study Clinical Trial Experience Survey							X
Urine pregnancy test (women of childbearing potential only)[h]	X					X	X
Blood Chemistry and Hematology (CBC, CMP)	X				X	X	
Hemoglobin A1c	X						

Table 2: Schedule of Assessments (Continued)

		Treatment Period					Follow Up Without Treatment
Study Procedures	**Visit 1 / Screening Up to 15 Days Before Day 1**	**Visit 2 Baseline / Day 1**	**Visit 3 Day 7 ± 2 days**	**Visit 4 Day 14 ± 2 days**	**Visit 5 Month 1 ± 3 days**	**Visit 6 Month 2 ± 3 days**	**Visit 7 Month 3 ± 3 Days/ Early Discontinuation**
Urinalysis	X				X	X	
Adverse events (AEs)	X	X	X	X	X	X	X
[redacted]							
[redacted]							

[a] [redacted]

[h] Urine pregnancy test (women of childbearing potential only) may be repeated at each visit as per request of IRB/IECs or at the Investigator's discretion.

[i] Only patients fulfilling eligibility criteria will be enrolled and receive the study medication.

[redacted]

2. INTRODUCTION

2.1. Background

Presbyopia refers to a condition in which the accommodative function of the eye gradually decreases with age, making it difficult to focus on close objects. Presbyopia is a common visual system condition in which the aging eye gradually develops impairment in the ability to focus on near and intermediate objects, starting around 40 years of age (Stokes et al., 2022).

Santen is developing STN1013600 (DE-136), a formulation of Ursodeoxycholic Acid (UCDA) as an ophthalmic solution for the treatment of presbyopia. This study is being conducted to evaluate the safety and efficacy of STN1013600 ophthalmic solution in subjects with presbyopia.

This Phase IIa study 1013600IN (OPSIS) will evaluate the efficacy and safety of ophthalmic solution of DE-136 0.1% and 0.3% administered BID for the treatment of Presbyopia. [redacted]

2.2. Study Rationale

In 2015, an estimated 1.1–1.8 billion people worldwide were impacted by presbyopia, and the number is predicted to reach 2.1 billion by 2030 (Stokes et al., 2022). Until recently the treatment and management options for presbyopia were either optical techniques, *e.g.,* spectacles and contact lenses, or surgical interventions, *e.g*., laser in-situ keratomileusis (Presby LASIK), corneal inlay, and multi-focal intraocular lenses. However, these options have disadvantages, including reduced visual quality at one or more distances (Charman, 2014) and the risks associated with surgical intervention. Hence, there is an unmet need for a noninvasive treatment that is effective in restoring accommodative function and providing good vision at all distances (Grzybowski et al., 2020).

Pharmacological treatment for presbyopia has the potential to address this unmet need. Two different classes of drugs have been investigated for this purpose. The recent approval in 2021 of VUITY® (pilocarpine hydrochloride ophthalmic solution) represents the first in this class of miotics. These drugs increase the depth of focus by decreasing pupil size, creating a pinhole effect.

The long-term outcome on efficacy, safety, and acceptance of VUITY as a standard of care remains to be evaluated.

The other class of drugs in development for presbyopia postulates that lens stiffening and loss of flexibility result in decreased distortion of the lens during accommodation. Although various factors may contribute to the lowering of accommodative function, sclerosis of the lens via oxidation-induced disulfide bonds between the crystalline lens protein seems to be a significant factor (Rowen, 2020, Wolffsohn et al., 2019). Garner et al. found that the antioxidant lipoic acid, reduced disulfide bonds in lens proteins of aged mice and increased lens elasticity in a

concentration-dependent manner. Further, synthesized choline esters were shown to improve the translocation of lipoic acid to the aqueous humor for a more efficient effect (Garner et al., 2016).

[redacted]

2.3. Benefit/Risk Assessment

Risks associated with participation in this study are considered to be minimal. [redacted]

[redacted]

3. OBJECTIVES AND ENDPOINTS

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy Objective: To assess the efficacy of two concentrations of STN1013600 ophthalmic solution (0.1% and 0.3%) twice daily dosing when compared to Placebo in subjects aged from 47 to 55 years with presbyopia.	**Primary Efficacy Endpoint:** • Mean change from baseline in Binocular DCNVA at Month 2
Secondary Efficacy Objective: To assess the dose response of STN1013600 ophthalmic solution.	**Secondary Efficacy Endpoints:** • Mean change from baseline in Study Eye DCNVA at all visits • Mean change from baseline in Binocular DCNVA at all visits • Proportion of subjects who improve 1/2/3-lines or more in Study Eye and Binocular DCNVA at each visit • Mean change from baseline in quality of life assessed with Near Activity Visual Questionnaire (NAVQ) at Month 2 and Month 3 • Subject treatment satisfaction as assessed by Patient Global Rating of Treatment at Month 2

Table 3: Objectives and Endpoints (Continued)

Objectives	Endpoints
Safety Objective: To assess the safety of two concentrations of STN1013600 ophthalmic solution (0.1% and 0.3%) twice daily dosing when compared to Placebo in subjects aged from 47 to 55 years with presbyopia.	**Safety Endpoint:** Safety of STN1013600 will be assessed by adverse events (AEs), Intra-ocular Pressure (IOP), slit-lamp bio-microscopy, ophthalmoscopy, and laboratory tests (serum chemistry, hematology, and urinalysis).
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase IIa, randomized, double-masked, placebo-controlled, parallel-group study assessing the efficacy and safety of STN1013600 ophthalmic solution (0.1% and 0.3%) in subjects with Presbyopia.

Approximately 75 subjects who meet all eligibility criteria at Visit 1 (Screening) will be randomized at Visit 2 (Baseline) in a 2:2:1 ratio to one of the following three treatment arms:

- 0.1% STN1013600 ophthalmic solution BID (08:00 & 20:00 ± 60 min)
- 0.3% STN1013600 ophthalmic solution BID (08:00 & 20:00 ± 60 min)
- Placebo (vehicle) BID (08:00 & 20:00 ± 60 min)

If both eyes of a subject qualify for the study, then the eye with the worse DCNVA will be determined as the study eye. If DCNVA in both qualifying eyes is the same, then the right eye should be designated as the study eye.

Subjects will be treated for 2 months, followed by 1 month safety follow-up without treatment. The total duration of participation for each subject is expected to be approximately 15 weeks.

4.2. Scientific Rationale for Study Design

The purpose of this phase IIa study is to evaluate the safety and efficacy of 2 doses of STN1013600 in subjects with presbyopia. The randomized, placebo-controlled, parallel-group study design is standard for the demonstration of efficacy and safety in multiple-arm clinical trials. The study is randomized and double masked to minimize bias and to reduce the risk of a placebo effect. [redacted]

4.3. Justification for Dose

[redacted]

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including Month 3 Visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. [redacted]
2. Phakic presbyopic subjects, Male or Female between 47 and 55 years of age
3. Distance-corrected near visual acuity (DCNVA) for each eye, as well as for binocular vision, 70 EDTRS letters or worse (equivalent to 0.3 logMAR or worse; or 20/40 Snellen or worse) at 40 cm. To be reconfirmed at Visit 2 (Baseline).
4. Best-corrected distance visual acuity (BCDVA) for each eye of 85 ETDRS letters or better (equivalent to 0.00 logMAR or better; or 20/20 Snellen or better) at 4 m. To be reconfirmed at Visit 2 (Baseline).
5. [redacted]

[redacted]

6. [redacted]
7. [redacted]
8. [redacted]

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Ocular Conditions

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. [redacted]
7. [redacted].
8. [redacted]

9. [redacted]
10. [redacted]
11. [redacted]
12. [redacted]
13. [redacted]
14. [redacted]
15. [redacted]
16. Secondary cause of presbyopia in either eye as assessed by investigator (*e.g.*, damage to lens, zonules or ciliary muscle, multiple sclerosis, cardiovascular accidents, vascular insufficiency, myasthenia gravis, anemia, influenza, measles).
17. Any history of ocular surgery (including ocular laser surgery) in either eye or plan of ocular surgery (including ocular laser surgery) during the course of the study.
18. Prior invasive therapy for presbyopia (*e.g.*, ciliary body electrostimulation, corneal implants).
    - Prior medical therapy for Presbyopia (*e.g.*, supplements, miotic medications, training exercises) within 30 days of Visit 1 (Screening)
    - Subjects with prior non-surgical optical correction (*e.g.*, corrective eyeglasses) are eligible for the study

[redacted]

19. [redacted]
20. [redacted]
21. [redacted]

22. [redacted]

23. [redacted]

24. [redacted]

25. [redacted]

26. [redacted]

27. [redacted]

28. [redacted]

29. [redacted]

30. [redacted]

31. [redacted]

32. [redacted]

33. [redacted]

5.3. Contraception Requirements

[redacted]

[redacted]

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to a study medication/entered in the study. [redacted]

[redacted]

6. STUDY INTERVENTION

6.1. Study Medications Administered

Table 4: Descriptions of Study Medications

ARM Name	STN1013600, 0.3%	STN1013600, 0.1%	Placebo
Intervention Name	STN1013600	STN1013600	Placebo
Type	Drug	Drug	Drug
Dose Formulation	Ophthalmic Solution	Ophthalmic Solution	Ophthalmic Solution
Unit Dose Strength(s)	0.3%	0.1%	Not Applicable
Dosage Level(s)	One drop, BID, both eyes throughout the 2-month Treatment Period	One drop, BID, both eyes throughout the 2-month Treatment Period	One drop, BID, both eyes throughout the 2-month Treatment Period
Route of Administration	Topical ocular	Topical ocular	Topical ocular
Use	Experimental	Experimental	Placebo- comparator
IMP and NIMP	IMP	IMP	IMP

Table 4: Descriptions of Study Medications (Continued)

ARM Name	STN1013600, 0.3%	STN1013600, 0.1%	Placebo
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Study Medication Storage

[redacted]

6.2.2. Study Medication Administration

During the Double-Masked Treatment Period, subjects will instill one drop of study medication in each eye at approximately 08:00 ± 60 min and 20:00 ± 60 min daily from Visit 2 (Baseline) to Visit 6 (Month 2). [redacted]

6.2.3. Study Medication Accountability

The Principal Investigator is responsible for ensuring that an inventory is conducted upon receipt of the clinical supplies. [redacted]

[redacted]

6.2.4. Study Medication Handling and Disposal

[redacted]

6.3. Measures to Minimize Bias: Randomization and Masking

[redacted]

This is a double-masked study. [redacted]

6.4. Study Intervention Compliance

To obtain reliable efficacy and safety data, the following precautions will be taken to ensure compliance with the study medication during the study:

- Subjects will receive verbal and written instructions for proper instillation of the study medication, the dosing regimen, and the conditions of the study medication storage.
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Subjects may be discontinued from the study at the discretion of the investigator if the subject cannot be brought into compliance.

A record of the number of kit cartons dispensed to and taken by each subject must be maintained and reconciled with study medication and compliance records. Medication start and stop dates, including dates for medication delays and/or dose reductions will also be recorded on the CRF.

6.5. Concomitant Therapy

Medication or therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator. Subjects may continue participation in the study if the instituted medication or therapy will not interfere with the evaluation of the study medication. Whenever possible, medications should be administered in dosages that remain constant throughout the study. Any treatment other than the study medication during the study duration will be considered as a concomitant treatment. The information of concomitant treatment must be recorded in the subject's source documents and on the eCRF.

- Concomitant medication: name of medication, route of administration, treated eye(s) (if applicable), dose, frequency, indication, start date, and stop date.

- Concomitant therapy: name of therapy, treated eye(s) (if applicable), indication, start date, and stop date.

6.5.1. Collection of Prior and Concomitant Medication Information

At Screening, information on prior and concomitant medications taken within the previous 90 days will be collected and to satisfy assessment of study Inclusion and Exclusion Criteria. At each study visit, subjects should be questioned concerning any new medications or changes in their current medications since their previous study visit and the information should be recorded in the eCRF. For all medications, the generic name, indication, route of administration, frequency, dose, start date, and stop date (if applicable) will be collected; for combination products, the brand name will also be documented.

6.5.2. Prohibited Medications or Therapies

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Any history of ocular surgery (including ocular laser surgery) in either eye or plan of ocular surgery (including ocular laser surgery) during the course of the study.
- Prior invasive therapy for presbyopia (*e.g.*, ciliary body electrostimulation, corneal implants).
  - Prior medical therapy for Presbyopia (*e.g.*, supplements, miotic medications, training exercises) within 30 days of Visit 1 (Screening)
  - Subjects with prior non-surgical optical correction (*e.g.*, corrective eyeglasses) are eligible for the study
- Subjects with any history or current use of contact lenses, or plan of use during course of study
- Current or planned participation in any other clinical study involving an investigational product or device within 4 weeks prior to Visit 1 or at any time during this study.

6.6. Rescue Medicine

Not applicable. There are no alternative standard medicinal therapies for the condition being treated.

6.7. Dose Modification

Dose modifications are not allowed in this study.

6.8. Intervention after the End of the Study

No subsequent intervention is planned for subjects after completing the study. Standard of care will resume at the investigator's discretion.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, study assessments should be completed per SoA including Exit Visit. All efforts should be made to complete an early discontinuation exit visit. If study medication is definitively discontinued and the subject has an AE related to study medication, he/she will remain in the study to be evaluated until the resolution of the AE. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Discontinuation of study intervention for any safety concern should be considered if the investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified (including, but not limited to clinically significant changes from baseline in any laboratory evaluation) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an AE.

7.1.1. Temporary Discontinuation

Temporary discontinuation of study medication is not applicable in this study.

7.1.2. Rechallenge

Not applicable to this study.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Visit Details

- Study procedures and their timing are summarized in the SoA (Table 2). Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (*e.g.*, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

[redacted]

[redacted] The primary efficacy analysis will be assessed at the 2 Month visit.

8.1.1. Visit 1 (Screening)

- Explain the purpose and conduct of the study to the subject and obtain written individual informed consent. Informed consent for the optional BOSS™ testing must be obtained prior to lens elasticity measurement at Visit 1 (Screening). Ensure the subject understands that if he/she does not wish to participate in BOSS™ testing that their decision will have no influence on their participation in the main study. BOSS™ testing is only available at a subset of clinical sites.

- Prepare the list of screening/registration of subjects.
- [redacted]
- Obtain demographics.
- Obtain medications, procedures/therapies, and medical and surgical history including all lifetime ocular medical history to the extent possible, non-ocular medical history within 10 years, diagnosis, ocular surgical history, current ocular, and systemic conditions.
- Measure vital signs
- Measure height and weight
- [redacted]
- Obtain urine and perform a urine pregnancy test, if the subject is a female of child-bearing potential.
- Instruct subject to complete clinical lab collection (urinalysis, hematology, chemistry and HbA1c). Results of clinical lab must be received and reviewed prior to Visit 2 (Baseline).
- Assess for adverse events (occurring after the signing of the informed consent)
- Assess eligibility of subject by reviewing the inclusion and exclusion criteria. A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure.
- Enter the subject information into the EDC system for Visit 1 (Screening) to obtain the subject ID

8.1.2. Visit 2 (Baseline, Day 1)

- [redacted]
- Measure vital signs
- Update concomitant medications and procedures/therapies
- [redacted]
- Measure pupil size
- Measure Intraocular Pressure
- [redacted]
- Assess for adverse events
- Perform final review of eligibility criteria. If all eligibility criteria, the subject will then be randomized, via IRT.
- [redacted]

8.1.3. Double-Masked Treatment Period, Visit 3 (Day 7)

- Measure vital signs
- Update concomitant medications and procedures/therapies

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Perform slit-lamp Biomicroscopy
- Measure pupil size
- Measure Intraocular Pressure
- [redacted]
- Assess for adverse events
- [redacted]

8.1.4. Double-Masked Treatment Period, Visit 4 (Day 14)

- Measure vital signs
- Update concomitant medications and procedures/therapies
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Perform slit-lamp Biomicroscopy
- Measure pupil size
- Measure Intraocular Pressure
- [redacted]
- Assess for adverse events
- [redacted]

8.1.5. Double-Masked Treatment Period, Visit 5 (Month 1)

- Measure vital signs
- Update concomitant medications and procedures/therapies
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Perform slit-lamp Biomicroscopy
- Measure pupil size
- Measure Intraocular Pressure
- [redacted]
- Instruct subject to complete clinical lab collection (urinalysis, hematology, and chemistry analysis).
- Assess for adverse events
- [redacted]

8.1.6. Double-Masked Treatment Period, Visit 6 (Month 2)

- [redacted]
- Measure vital signs
- Update concomitant medications and procedures/therapies
- [redacted]

- [redacted]
- Perform slit-lamp Biomicroscopy
- Measure pupil size
- Measure Intraocular Pressure
- [redacted]
- Obtain urine and perform a urine pregnancy test if the subject is a female of child-bearing potential.
- Instruct subject to complete clinical lab collection (urinalysis, hematology, and chemistry analysis).
- Assess for adverse events
- [redacted]

8.1.7. Double-Masked Treatment-free Period, Visit 7 (Month 3), Exit/Early Termination

- [redacted]
- Measure vital signs
- Update concomitant medications and procedures/therapies
- [redacted]

- [redacted]
- [redacted]
- Perform slit-lamp Biomicroscopy
- Measure pupil size
- Measure Intraocular Pressure
- [redacted]
- [redacted]
- Obtain urine and perform a urine pregnancy test if the subject is a female of child-bearing potential.
- Assess for adverse events
- Exit the subject from the study.

NOTE:

If the study medication administration is discontinued, then to the extent possible, all procedures for Study Exit/Early Termination as per SoA (Table 2) will be performed on the day of early termination. Subjects who are discontinued from the study early will not be replaced.

8.1.8. Unscheduled Visits

If subject requires an unscheduled visit, procedures and assessments will be performed as needed.

8.2. Safety Assessments

8.2.1. Vital Signs

- Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest in a seated position and in a quiet setting without distractions (*e.g.*, television, cell phones).
- Temperature will be collected as per site's standard of care.

8.2.2. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 1 month after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (*e.g.*, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3. Adverse Events and Serious Adverse Events

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.3.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study medication.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the Informed Consent Form (ICF) until subject withdrawal or the scheduled exit visit. (Note: Although AEs will be monitored for and collected prior to IP administration, the statistical data analysis will determine and summarize treatment-emergent AEs, *i.e.*, those AEs that began or worsened in severity after the first IP administration.)

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after

a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 10.3), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 10.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (*e.g.*, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy Testing, Monitoring, and Reporting

8.3.5.1. Pregnancy Testing

If the subject is a woman of child-bearing potential urine samples will be collected for pregnancy tests at screening and prior to IP administrations as specified in the SoA (Table 2). Samples will be analyzed at the site with results available prior to administration of IP.

8.3.5.2. Pregnancy Monitoring and Reporting Procedures

Pregnancy in female subjects and female partners of male subjects will be monitored starting from screening through the End of study duration/Exit/Early Termination visit.

[redacted]

8.3.6. Adverse Events of Special Interest

- [redacted]

[redacted]

8.4. Treatment of Overdose

The intervention in this study is a topical ophthalmic solution. Overdose of study medication is not anticipated. In case of any concerns regarding potential overdose, the Medical Monitor should be consulted.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

Not applicable.

8.8. Biomarkers

Not applicable.

8.9. Immunogenicity Assessments

Not applicable.

8.10. Health Economics/Medical Resource Utilization

Not applicable.

9. STATISTICAL CONSIDERATIONS

This section outlines the topics related to the statistical methods used in the design and analysis of the study. A more detailed description of all the analyses and methods is provided in the statistical analysis plan (SAP).

9.1. Statistical Hypotheses

The primary endpoint is change from baseline in binocular distance-corrected near visual acuity (DCNVA) at Month 2. [redacted]

[redacted]

[redacted]

9.2. Sample Size Determination

[redacted] Based on the feasibility of conducting the trial, a total of approximately 75 subjects will be randomized into a 2:2:1 ratio to 0.1% STN1013600, 0.3% STN1013600, and placebo arms. That is, an approximately 30 subjects and 15 subjects will be randomized into each of STN1013600 treatment arms and placebo arm, respectively.

[redacted]

[redacted]

9.3. Populations for Analyses

9.3.1. Safety Population

The Safety Population will include all randomized subjects who received at least one dose of the study medication. [redacted]

9.3.2. Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects who received at least one dose of study medications and provided at least one post-baseline efficacy measurement. [redacted]

9.3.3. Per-Protocol Set

Then Per-Protocol Set (PPS) is a subset of the FAS, restricted to the subjects who fulfill the protocol in terms of the eligibility, medications, and outcome measurement. [redacted]

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

[redacted]

9.4.2. Handling of Missing Values

[redacted]

For medical events including AEs and medical history, completely or partially missing onset and resolution dates will be imputed in a conservative fashion to be detailed in the SAP. Similar rules will be followed to impute the completely or partially missing start and end dates of non-study medications.

[redacted]

9.4.3. Primary Endpoint

The primary efficacy endpoint is change from baseline in binocular DCNVA at Month 2.[redacted]

9.4.4. Secondary Endpoints

[redacted]

Subgroup analyses may be performed for primary and secondary endpoints using descriptive statistics.

9.4.5. Exploratory Endpoints

[redacted]

9.4.6. Safety Analyses

All safety outcome measures will be summarized descriptively for the Safety Population. The safety outcome measures include AEs and evaluation with slit-lamp biomicroscopy,

ophthalmoscopy, intraocular pressure (IOP), pupil size and laboratory tests (serum chemistry, hematology, and urinalysis).

AEs will be coded using the latest version of MedDRA. Subjects with any AE(s) will be tabulated by system organ class (SOC) and preferred term specified in MedDRA dictionary. Similarly, subjects with any ocular and non-ocular AEs will be tabulated separately. AEs, ocular and non-ocular AEs will be summarized by relationship to treatment and maximum severity. In addition, SAEs, and discontinuations due to AEs will be summarized.

Safety parameters listed in safety assessments Section 8.2 will be summarized using descriptive statistics by actual treatment received. Changes from baseline in these safety parameters will also be summarized by treatment.

9.5. Interim Analyses

An interim analysis may be performed when the first 40 subjects complete Day 14 Visit. [redacted]

9.6. Santen Steering Committee (SSC)

An internal Santen steering committee (SSC) whose members will not be participating in the OPSIS study conduct will serve as an advisory board to the Santen management team. [redacted] The organization, responsibilities, and procedures of the SSC will be specified in a governing charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (*e.g.*, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Obligations of Investigators

The Principal Investigator must agree to the following obligations:

- Obtain informed consent from every subject before the subject's participation in any study-related activity and maintain records of consent as part of the study records.
- Obtain approval from the IRB or IEC before involving any subject in any study-related activity; submit verification of the approval to Santen; submit periodic progress reports (at least annually) and final report to IRB or IEC.
- Conduct the study according to the protocol and applicable regulations and inform Santen of all deviations from the protocol.
- Inform the IRB or IEC of all protocol amendments/modifications; send Santen a copy of the letter from the IRB or IEC approving the amendment/modification.
- Report to Santen any AEs and report to the IRB or IEC any reportable AEs that occur in the course of the investigation.
- Keep complete and accurate records of all clinical study data; maintain records of all materials submitted to the IRB or IEC and of all correspondence by the IRB or IEC regarding the study.
- Make study records available for inspection by Santen and representatives of regulatory agencies and the IRB or IEC; keep records until notified by Santen that they may be destroyed.
- Maintain proper control and documentation of all test and control articles.

- Submit to Santen and/or maintain the following:

  I. Before the beginning of the study provide to Santen:

  a. A signed Form FDA 1572, Statement of Investigator, if applicable.
  b. A signed Financial Disclosure Form.
  c. A current curriculum vitae (CV) if not submitted previously or if updated.
  d. CVs for all Sub-Investigators.
  e. A letter from the IRB or IEC indicating that the protocol was approved, including the name and address of the IRB or IEC.
  f. A copy of the consent form approved by the IRB or IEC.
  g. A list of current members of the IRB or IEC.
  h. A copy of the source data location list.
  i. A copy of delegation list/log.
  j. A copy of training log.

  II. While the study is in progress:

  a. Acknowledgment of receipt of the test and control articles; documentation of disposition of all test and control articles.
  b. eCRFs for each subject enrolled in the study.
  c. Information regarding all deviations from the protocol.
  d. Information regarding all AEs occurring to a subject while enrolled in the study.
  e. Annual progress report (if study is on-going for more than one year). Letter from the IRB or IEC indicating approval of the annual progress report.

  III. Upon completion of the study:

  a. Disposition of all used and/or unused test and control articles, as well as documentation of all and drug accountability.

10.1.3. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.
- The ICF will contain a separate section that addresses exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study period. A separate signature will be required to document a participant's agreement to comply with procedures for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.5. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6. Committees Structure

An SSC charter will be developed to document the structure, frequency of meetings and rules for this committee.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (*e.g.*, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (*e.g.*, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and contracts.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (*e.g.*, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator until notified by Santen that the records may be destroyed. No records may be destroyed during the retention period without the written approval of Santen. No records may be transferred to another location or party without written notification to Santen.

10.1.8. Source Documents

The Principal Investigator must maintain detailed source documents on all study subjects who provide informed consent. Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents include subject medical records, hospital charts, clinic charts, study files, as well as the results of diagnostic tests (*e.g.*, laboratory tests). Source documents are filed at the investigator's site.

The following minimum information should be entered into the subject's medical record:

- The date the subject entered the study and the subject number
- The study protocol number and the name of Santen
- The date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (*e.g.*, medical history, study procedures, and/or evaluations)
- The dates of all study-related subject visits (scheduled and unscheduled)
- Evidence that required procedures and/or evaluations were completed
- Use of any concomitant medications
- Documentation of study medication accountability
- Occurrence and status of any AEs
- The date the subject exited the study and a notation as to whether the subject completed or terminated early from the study, including the reason for early termination
- If unmasking at the site occurred, proper documentation and notifications were made

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study medication development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research

organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.10. Publication Policy

The existence of this clinical study is confidential, and it should not be discussed with persons outside of the study. [redacted]

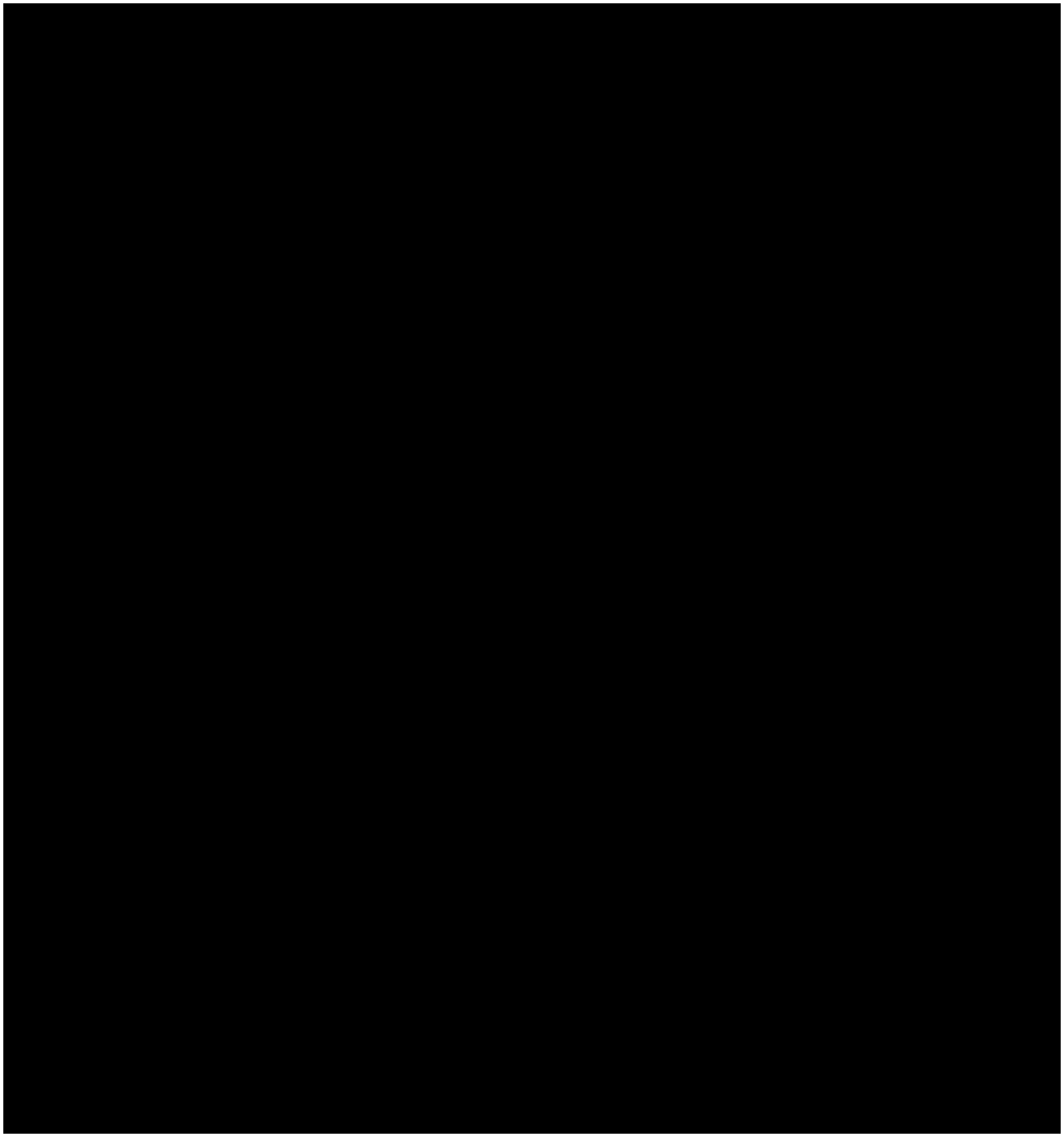
In signing this protocol, the Principal Investigator agrees to the release of the data from this study and acknowledges the above publication policy.

10.2. Appendix 2: Clinical Laboratory Tests

- [redacted]
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.

Table 5: Protocol-Required Safety Laboratory Assessments



10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (*e.g.*, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (*i.e.*, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (*e.g.*, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (*e.g.*, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (*e.g.*, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (*e.g.*, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

AE and SAE Recording

- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Santen in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Santen. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Santen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator’s Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Santen. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Santen.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

AE and SAE Recording
Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Santen to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Santen with a copy of any post-mortem findings including histopathology • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to Santen within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Santen via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Santen will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Santen Safety Team by telephone. • Contacts for SAE reporting can be found in Table 1.
SAE Reporting to Santen via Paper CRF (If Electronic Data Collection Tool is Unavailable)
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Santen Safety Team. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. Contacts for SAE reporting can be found in Table 1.

10.4. Procedures for Assessments

10.4.1. Symptom Assessment iN Dry Eye Questionnaire (SANDE)

[redacted]

[redacted]

10.4.2. Near Activity Visual Questionnaire

[redacted]

10.4.3. Objective Refraction

[redacted]

10.4.4. Subjective Refraction (Manifest Refraction)

[redacted]

10.4.5. Distance Corrected Near Visual Acuity (DCNVA)

The distance corrected near visual acuity (DCNVA) will be measured in right eye, left eye and both eyes at all visits using the distance manifest refraction. The total number of letters at 40 cm will be recorded. Refer to Visual Acuity Manual of Procedures for details of the visual acuity assessments.

10.4.6. Distance Corrected Intermediate Visual Acuity (DCIVA)

[redacted]

10.4.7. Best Corrected Distance Visual Acuity Testing (BCDVA)

The best-corrected distance visual acuity (BCDVA) will be recorded for right eye, left eye and both eyes at all visits using ETDRS charts. The total number of letters at 4 meters and 1 meter will be recorded. If a subject's visual acuity is so poor that he/she cannot read any chart letters when tested at 1 meter, then the subject's ability to count fingers, detect hand motion, or have

light perception should be evaluated. Refer to Visual Acuity Manual of Procedures for details of the visual acuity assessments.

10.4.8. Subjective Accommodative Amplitude Testing (Defocus Curve Testing)

[redacted]

10.4.9. Lens and Corneal Elasticity Testing

[redacted]

10.4.10. Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy examinations will be used to examine eye structures for both eyes during screening and at each follow-up study visit. Magnification will be consistent with standard clinical practice. The patient will be seated while being examined. Grading will be done using the following scales:

The lid, conjunctiva, cornea, iris, and lens will be observed and graded on a 4-point scale (0-3 scale). Anterior chamber cells and flare will be observed and graded using the SUN scale (0-4 scale).

Lid Hyperemia

None	(0) =	Normal
Mild	(1) =	Redness of most or all the lid(s) margin OR skin
Moderate	(2) =	Redness of most or all the lid(s) margin AND skin
Severe	(3) =	Marked diffuse redness of both lid(s) margin AND skin

Lid Edema

None	(0) =	Normal
Mild	(1) =	Localized to a small region of the lid(s)
Moderate	(2) =	Diffuse, most or all the lid(s) but not prominent/protruding
Severe	(3) =	Diffuse, most or all the lid(s) AND prominent/protruding

Conjunctival (Palpebral and Bulbar) Hyperemia

None	(0) =	Normal
Mild	(1) =	Slight localized injection
Moderate	(2) =	Pink color, confined to palpebral OR bulbar conjunctiva
Severe	(3) =	Red color of the palpebral AND/OR bulbar conjunctiva

Conjunctival Chemosis

None	(0) =	Normal
Mild	(1) =	Slight localized swelling
Moderate	(2) =	Mild/medium localized swelling or mild diffuse swelling
Severe	(3) =	Moderate diffuse swelling

Corneal Edema

None	(0) =	Normal
Mild	(1) =	Mild, diffuse stromal haze
Moderate	(2) =	Dense, diffuse stromal haze or bullae
Severe	(3) =	Dense, diffuse bullae or stromal haze AND stromal edema

Corneal Staining (with fluorescein)

None	(0) =	Normal
Mild	(1) =	Localized, occasional punctate staining
Moderate	(2) =	Localized, dense OR diffuse occasional punctate staining
Severe	(3) =	Diffuse, dense punctate staining which may be confluent staining

Keratic Precipitate

None	(0) =	Normal
Mild	(1) =	Slight pigmentation or keratic precipitate
Moderate	(2) =	Moderate pigmentation or keratic precipitate
Severe	(3) =	Dense pigmentation or keratic precipitate

Anterior Synechiae of Iris

None	(0) =	No anterior synechiae of iris is found
Mild	(1) =	<25% anterior synechiae of iris is found
Moderate	(2) =	25% to 50% anterior synechiae of iris is found
Severe	(3) =	>50% anterior synechiae of iris is found

Posterior Synechiae of Iris

None	(0) =	No posterior synechiae of iris is found
Mild	(1) =	<25% posterior synechiae of iris is found
Moderate	(2) =	25% to 50% posterior synechiae of iris is found
Severe	(3) =	>50% posterior synechiae of iris is found

Lens

The lens will be noted as phakic, aphakic, or pseudophakic. Phakic lens will be graded as described below:

None (0) = No lens discoloration nor opacification

Mild (1) = Yellow lens discoloration or small lens opacity (axial or peripheral)

Moderate (2) = Amber lens discoloration or medium lens opacity (axial or peripheral)

Severe (3) = Brunescent lens discoloration or complete lens opacification (no red reflex)

Anterior Chamber Cells

(0) = No cells

(0.5) = 1-5 cells

(1) = 6-15 cells

(2) = 16-25 cells

(3) = 26-50 cells

(4) = >50 cells

Anterior Chamber Flare

(0) = None

(1) = Faint

(2) = Moderate (iris/lens details clear)

(3) = Marked (iris/lens details hazy)

(4) = Intense (fibrin/plastic aqueous)

10.4.11. Pupil Measurement

Pupil measurement will be performed with ambient lighting conditions (10-12 lux) with an automated device. The same device should be used for all visits on a subject.

10.4.12. Tear Film Break Up Time (TFBUT)

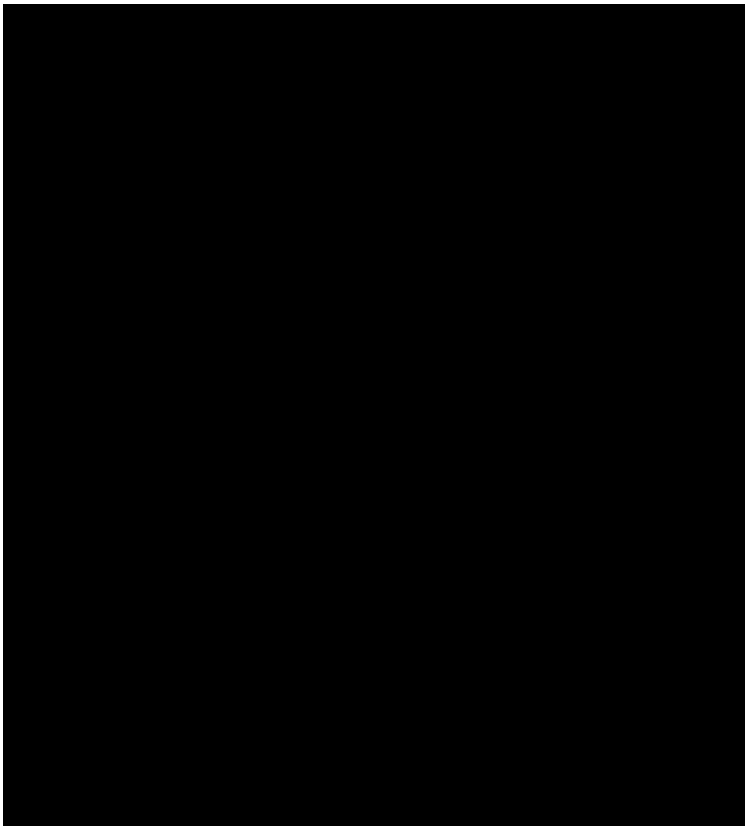
Tear break-up time (TBUT) will be measured by determining the time to tear break-up. The TBUT will be performed with fluorescein strips with sterile saline. To thoroughly mix the fluorescein with the tear film, the patient will be instructed to blink several times. In order to achieve maximum fluorescence, the examiner should wait approximately 30 seconds after instillation before evaluating TBUT. With the aid of a slit lamp using cobalt blue illumination, the examiner will monitor the integrity of the tear film, noting the time it takes to form lacunae

(clear spaces in the tear film) from the time that the eye is opened after the last blink. The TBUT will be measured twice during the first minute after the instillation of the fluorescein. If the 2 readings differ by more than 2 seconds, then a third reading will be taken.

The TBUT value will be the average of the 2 or 3 measurements.

10.4.13. Corneal Fluorescein Staining (CFS) Assessment with Oxford Scale

[redacted]



10.4.14. Intraocular Pressure (IOP)

Intraocular Pressure (IOP) will be measured using a Goldmann Applanation Tonometer during screening and at each follow-up study visit. The investigator's standard technique will be used throughout the study. [redacted]

[redacted]

All tonometers must be calibrated according to manufacturer's instructions.

10.4.15. Ophthalmoscopy

[redacted]

Health of the optic nerve with cup to disc ratio and abnormality in retina, macula, choroid, and vitreous will also be evaluated across all visits.

10.4.16. Cycloplegic Refraction

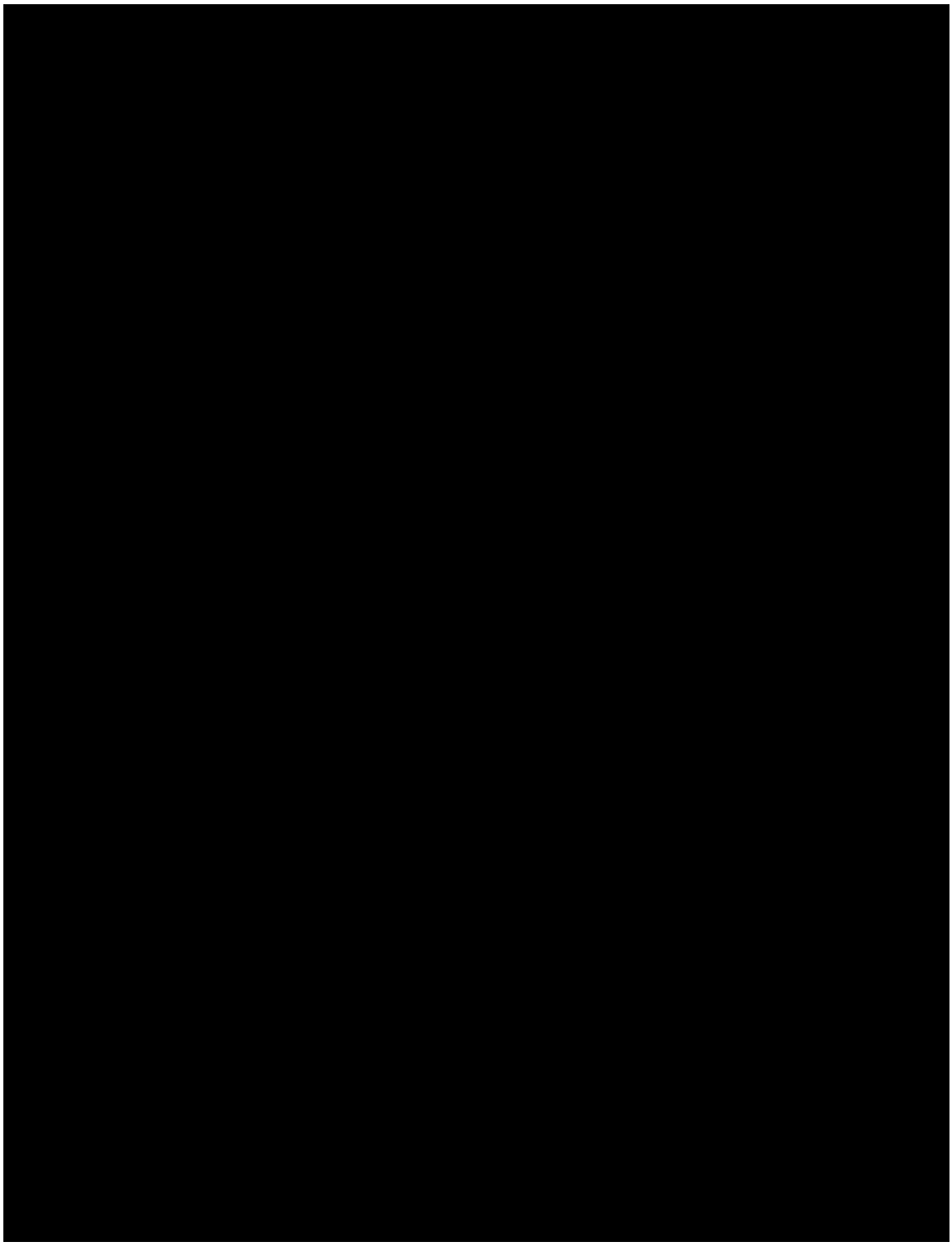
[redacted]

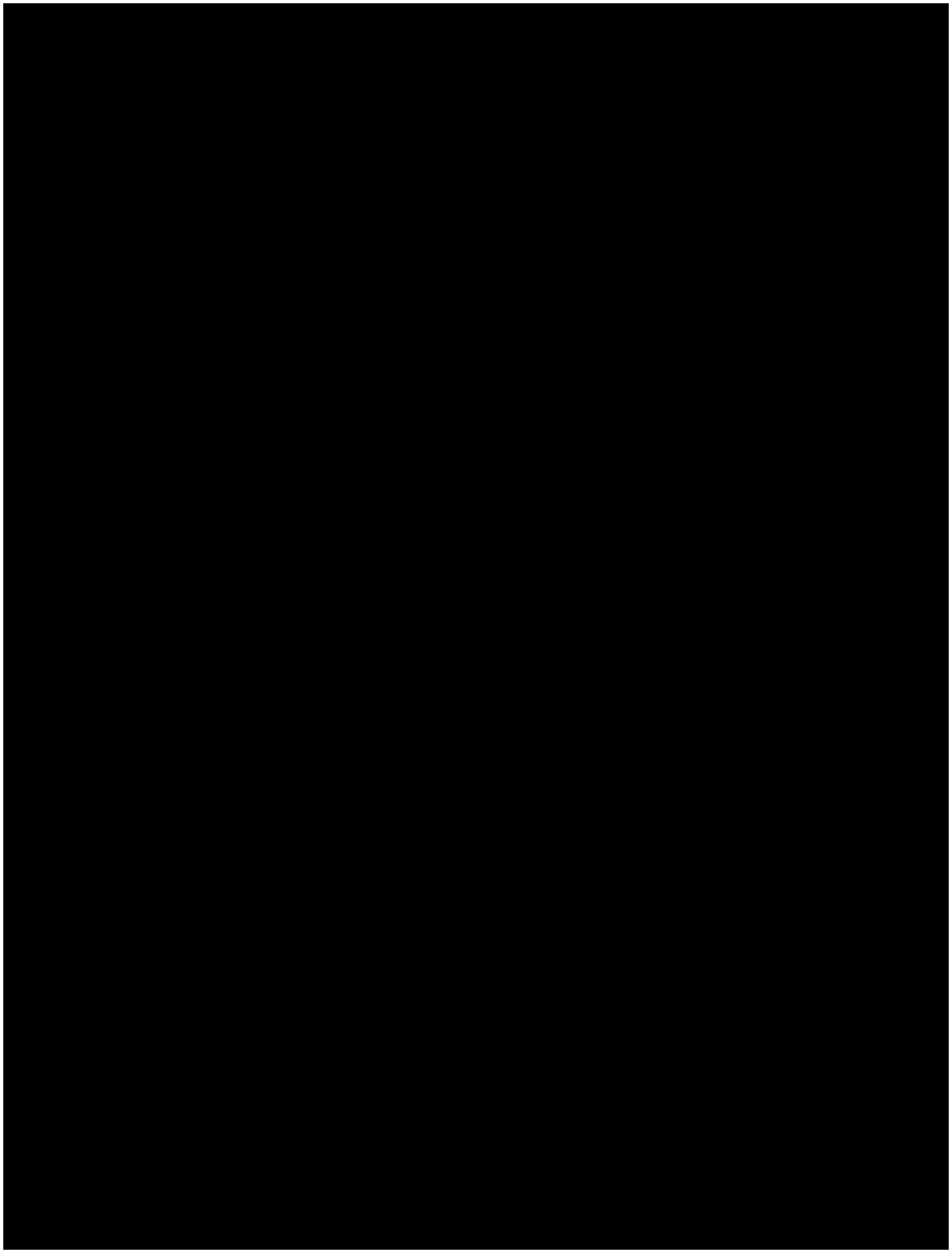
10.4.17. Patient Global Rating of Treatment

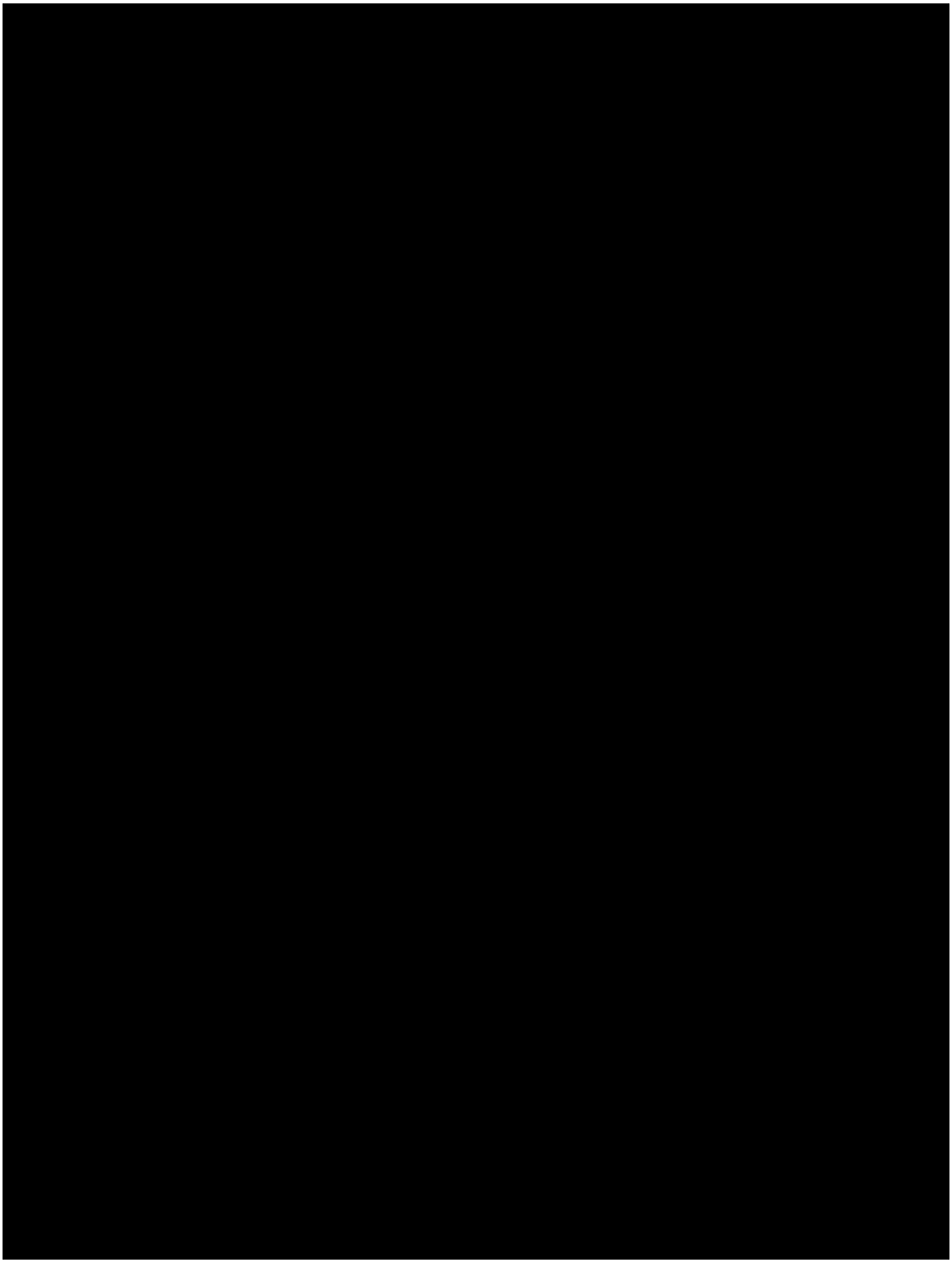
[redacted]

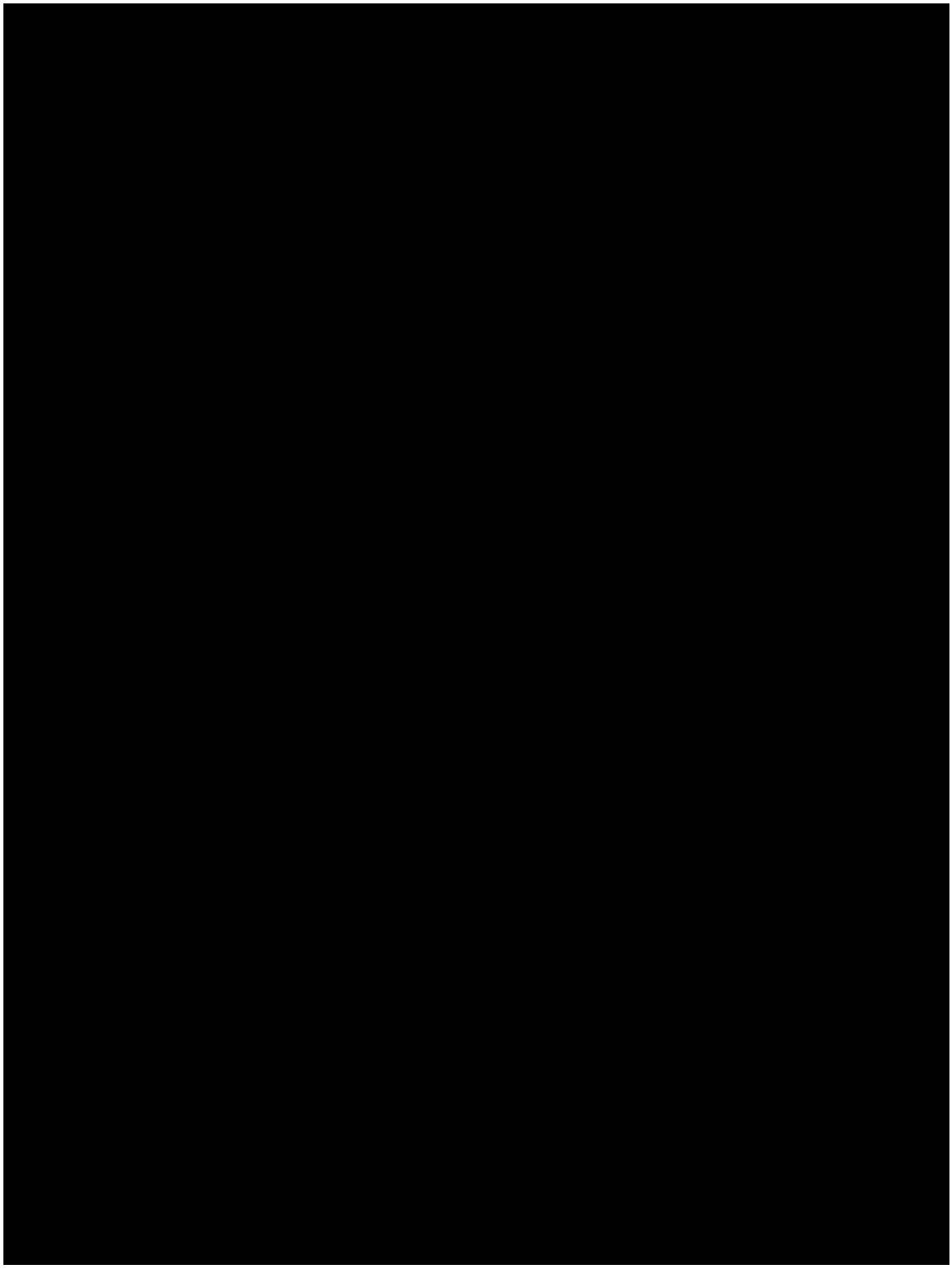
10.4.18. Post-Study Clinical Trial Experience Survey

[redacted]









10.4.19. Vital Signs

Vital signs consist of blood pressure, heart rate and temperature and will be collected at all visits. Blood pressure should be measured only after the subject has been in a sitting position for at least 5 minutes and will be recorded in millimeters of mercury (mmHg). Measurement with an automated sphygmomanometer is acceptable. Heart rate should be measured only after the subject has been in a sitting position for at least 2 minutes and will be recorded in beats per minute (bpm). Temperature will be collected as per site's standard of care.

10.5. Symptom Assessment iN Dry Eye Questionnaire (SANDE)

10.6. Near Activity Visual Questionnaire

10.7. Appendix 9: Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse Events
BCDVA	Best Corrected Distance Visual Acuity
BID	Twice a Day
BOSS/BOSS™	Brillouin Optical Scanner System
CFS	Corneal Fluorescein Staining
COVID	Coronavirus disease
D	Diopter
DCIVA	Distance corrected intermediate visual acuity
DCNVA	Distance corrected near visual acuity
eCRF	Electronic care report forms
ESI	Events of Special Interest

Appendix 9: Abbreviations (Continued)

Abbreviation or Term	Definition/Explanation
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Products
IOP	Intraocular Pressure
IRB	Institutional Review Board
logMAR	Logarithm of the Minimum Angle of Resolution
IRT	Interactive Response Technology
NIMP	Non-investigational Medicinal Products
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mmHg	millimeters of mercury
MMRM	Mixed-effects Model for Repeated Measures
NAVQ	Near Activity Visual Questionnaire
OD	Right Eye
OS	Left Eye
OU	Both Eyes
SAE	Serious Adverse Event
SANDE	Symptom Assessment iN Dry Eye Questionnaire
SAP	Statistical Analysis Plan
SOC	System Organ Class
TBUT	Tear breakup test
UCDA	Ursodeoxycholic Acid

10.8. Appendix 10: Protocol Amendment History

Not applicable. This is the first version of the protocol.

11. REFERENCES

1. Charman, W. N. (2014) Developments in the correction of presbyopia I: spectacle and contact lenses. Ophthalmic Physiol Opt.34(1):8-29.

2. Garner, W. H., Garner, M. H. (2016) Protein Disulfide Levels and Lens Elasticity Modulation: Applications for Presbyopia. Invest Ophthalmol Vis Sci.57(6):2851-63.

3. Grzybowski, A., Markeviciute, A., Zemaitiene, R. (2020) A Review of Pharmacological Presbyopia Treatment. Asia Pac J Ophthalmol (Phila).9(3):226-33.

4. Korenfeld, M. S., Robertson, S. M., Stein, J. M., Evans, D. G., Rauchman, S. H., Sall, K. N., Venkataraman, S., Chen, B. L., Wuttke, M., Burns, W. (2021) Topical lipoic acid choline ester eye drop for improvement of near visual acuity in subjects with presbyopia: a safety and preliminary efficacy trial. Eye (Lond).

5. Qi, H. P., Wei, S. Q., Gao, X. C., Yu, N. N., Hu, W. Z., Bi, S., Cui, H. (2012) Ursodeoxycholic acid prevents selenite-induced oxidative stress and alleviates cataract formation: In vitro and in vivo studies. Mol Vis.18:151-60.

6. Rowen, S. (2020) Pharmacologic Solutions to Presbyopia. Cataract & Refractive Surgery Today.

7. Stokes, J., Shirneshan, E., Graham, C. A., Paulich, M., Johnson, N. (2022) Exploring the Experience of Living with and Managing Presbyopia. Optom Vis Sci.99(8):635-44.

8. Wolffsohn, J. S., Davies, L. N. (2019) Presbyopia: Effectiveness of correction strategies. Prog Retin Eye Res.68:124-43.